Greater clinical benefit with tiomolibdate choline versus standard of care in neurologic WD patients in the Phase 3 FoCus Trial

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Introduction

ALXN1840 (tiomolibdate choline, TMC), is a novel first-in-class Albumin Tripartite Complex (ATC) activator under investigation for the treatment of Wilson disease (WD). WD is a rare genetic disorder of copper overload. ALXN1840 rapidly mobilizes and tightly sequesters excess copper in ATCs, suppressing its redox reactivity, limiting oxidative damage, and blocking transport across the blood–brain barrier. Clinical data demonstrate that ALXN1840 improves copper balance by increasing fecal copper excretion. In the phase III pivotal trial, ALXN1840 demonstrated rapid and sustained copper mobilization significantly greater than standard of care (SoC) over 48 weeks in both previously treated and untreated patients. Durable clinical improvement and a favorable tolerability and safety profile were observed across > 6 years of treatment.

Methods

The Phase 3 FoCus RCT (NCT03403205) enrolled 207 patients with WD to TMC (n=137) or standard of care (SoC, n=70) for 48 weeks, with an optional 5-year extension on TMC. Over half of enrolled patients (TMC: n=77; SoC: n=35) demonstrated neurological symptoms at baseline, defined as baseline Unified WD Rating Scale (UWDRS) Part III score greater than the minimum clinically important difference (MCID) of 4.668. UWDRS Part III assessments during the trial were rater-blinded. All analyses conducted on patients with data available.

Significantly Less Neurologic Worsening on TMC vs. SoC

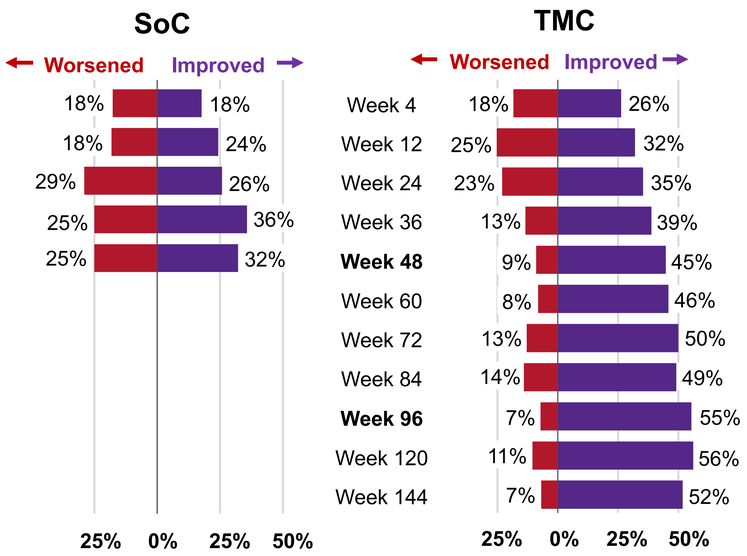
UWDRS Part III
Responder rates at Week 48

SoC	TMC
32% improved	45% improved
25% worsened*	9% worsened*

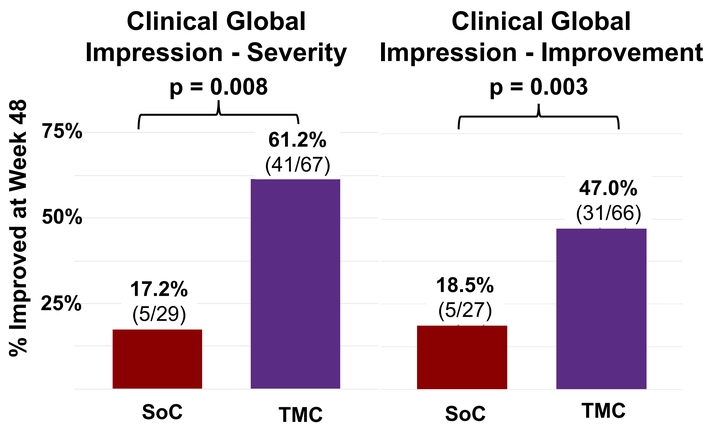
* = p < 0.05 for TMC vs. SoC

Results

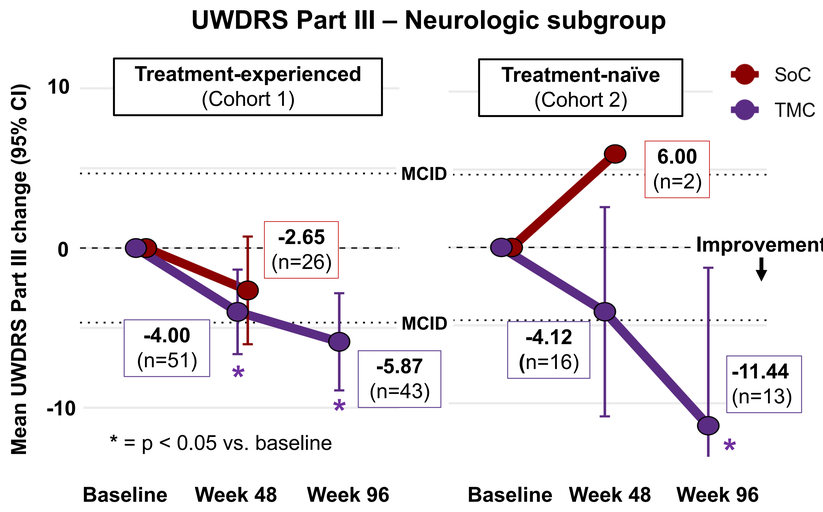
More Neurologic Improvement over Time on TMC vs SoC



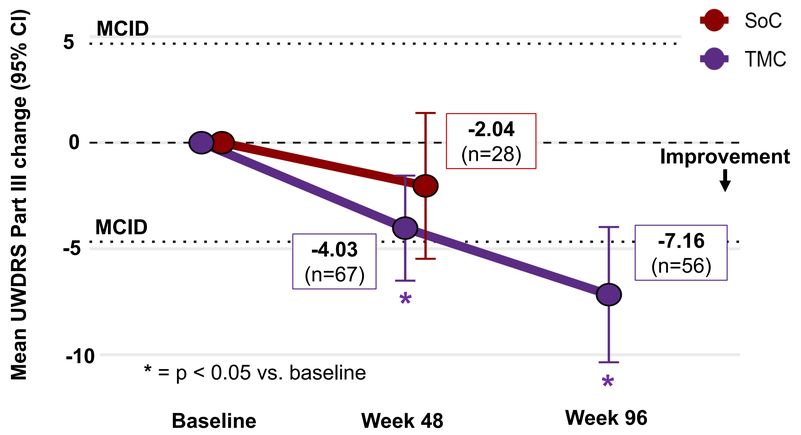
Greater Clinical Improvement on TMC vs. SoC at Week 48



Neurologic Benefit Increases over Time on TMC Regardless of Cohort



UWDRS Part III – Cohort 1 and 2 Combined



Safety

TMC showed a favorable safety profile across all treated patients with WD in Phase 2 & Phase 3 studies. Very few patients (~1%) experienced a neurologic or psychiatric SAE related to TMC. No deaths occurred that were deemed related to TMC.

Serious Adverse Events (SAEs) on TMC	
Number of patients	266
Median time on treatment (years)	2.58
Total **patient-years** (PYs)	645.6
Patients with **any drug-related SAE**	13 (4.9%)
Neurologic	2 (0.8%)
Psychiatric	1 (0.4%)

Data through 01-Sep-2022.

Conclusions

In WD patients with neurologic symptoms at baseline, 48 weeks of treatment with TMC led to greater clinical and neurologic benefit and less worsening compared to SoC. Greater neurologic benefit was observed in the TMC group regardless of WD treatment history. Continued improvement was sustained through long-term follow-up. These findings demonstrate that TMC improves neurologic outcomes in patients with WD presenting with neurologic symptoms.

References & Acknowledgements

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